CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074641

Trade Name : SELEGILINE HYDROCHLORIDE

Generic Name: Selegiline Hydrochloride Tablets 5mg

Sponsor : Lederle Laboratories

Approval Date: August 2, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074641

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074641

APPROVAL LETTER

ANDA 74-641

AUG 2 1996

Lederle Laboratories
Attention: Nicholas C. Tantillo
401 N. Middletown Road
Pearl River, NY 10965-1299

Dear Sir:

This is in reference to your abbreviated new drug application dated March 3, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Selegiline Hydrochloride Tablets USP, 5 mg.

Reference is also made to your amendments dated October 6 and November 20, 1995 and April 4, 15 and 30, 1996 and July 18, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Selegiline Hydrochloride Tablets USP, 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Eldepryl® Tablets, 5 mg of Somerset Pharmaceuticals Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 8/2/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074641

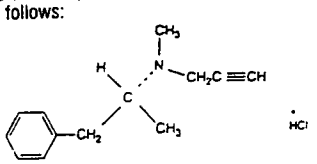
FINAL PRINTED LABELING

SELEGILINE HYDROCHLORIDE TABLETS, USP

DESCRIPTION:

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl.

The chemical name is: (R)-(-)-*N*,2-dimethyl-*N*-2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol. The structural formula is as follows:



$C_{13}H_{17}N \cdot HCl$ M.W. 223.75

Each tablet, for oral administration, contains 5 mg selegiline hydrochloride. Inactive ingredients: citric acid, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's Disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for type B than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a 'hypertensive crisis,' the so-called 'cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation — e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc.— they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane-bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons.

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). **In short, attention to the dose-dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)**

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease:

Many of the prominent symptoms of Parkinson's Disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's Disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is 'wearing off'), and is often accompanied by side effects (e.g., dyskinesia, akinesias, on-off phenomena, freezing, etc.).

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegiline's benefit in Parkinson's Disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's Disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination — ADME):

Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available.

Data obtained in a study of 12 healthy subjects that was intended to examine the effects of selegiline on the ADME of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethyldeprenyl, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites.

In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these

conditions, the mean trough serum levels for amphetamine were 3.5 ng/mL and 8.0 ng/mL for methamphetamine; trough levels of N-desmethyldeprenyl were below the levels of detection.

The rate of MAO B regeneration following discontinuation of treatment has not been quantitated. It is this rate, dependent upon de novo protein synthesis, which seems likely to determine how fast normal MAO B activity can be restored.

INDICATIONS AND USAGE:

Selegiline hydrochloride tablets are indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

Selegiline hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline is contraindicated for use with meperidine. This contraindication is often extended to other opioids. (See **Drug Interactions**.)

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (Phenelzine, Tranylcypromine). A similar reaction has been reported for a patient on amitriptyline and selegiline. Another patient receiving protriptyline and selegiline developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of selegiline and tricyclic antidepressants as well as selegiline and selective serotonin reuptake inhibitors. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline.

PRECAUTIONS:

General:

Some patients given selegiline may experience an exacerbation of levodopa-associated side effects, presumably due to the increased amounts of dopamine reaction with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline therapy. Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI-induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests:

No specific laboratory tests are deemed essential for the management of patients on selegiline. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:

The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination (see **CONTRAINDICATIONS**). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and selegiline and selective serotonin reuptake inhibitors and selegiline. (See **WARNINGS** for details.) One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in *Salmonella typhimurium* and an *in vivo* chromosomal aberration assay. While these studies provide some reassurance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed.

The effect of selegiline on fertility has not been adequately assessed.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12, and 35 times the human therapeutic dose on a mg/m^2 basis. No teratogenic effects were observed in a study of

embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m^2 basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increases in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m^2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether selegiline is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use:

The effects of selegiline hydrochloride in pediatric patients have not been evaluated.

ADVERSE REACTIONS:

Introduction:

The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris, and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss.

Experience with selegiline obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo-controlled trial performed in patients with Parkinson's Disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N=49	placebo N=50
Nausea	10	3
Dizziness/Lightheadedness/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System:

Motor/Coordination/Extrapyramidal:

increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric:

hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation:

headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers,

CODE INSERTED HERE

taste disturbance.

Autonomic Nervous System:

dry mouth, blurred vision, sexual dysfunction.

Cardiovascular:

orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal:

nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

Genitourinary/Gynecologic/Endocrine:

slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

Skin and Appendages:

increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous:

asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:

The following experiences were described in spontaneous post-marketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline hydrochloride.

CNS:

Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE:

Selegiline:

No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l-selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's Disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine (PARNATE), isocarboxazid (MARPLAN), and phenelzine (NARDIL)].

Overdose with Non-Selective MAO Inhibition:

NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions For Overdose:

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

Selegiline hydrochloride tablets are intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of selegiline hydrochloride is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo-controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

HOW SUPPLIED:

Selegiline Hydrochloride Tablets, USP 5 mg are white, round, unscored tablets engraved "LL" on one side and "S11" on the other side. They are supplied as:

NDC 0005-3254-38 — Bottle of 30s with CRC
NDC 0005-3254-32 — Bottle of 60s with CRC
NDC 0005-3254-42 — Bottle of 90s with CRC
NDC 0005-3254-43 — Bottle of 100s with CRC
NDC 0005-3254-48 — Bottle of 120s with CRC
NDC 0005-3254-23 — Bottle of 100s
NDC 0005-3254-31 — Bottle of 500s
NDC 0005-3254-34 — Bottle of 1000s

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

STANDARD PRODUCTS

LEDERLE LABORATORIES
A Division of American Cyanamid Company
Pearl River, NY 10965

CI 4647 Issued June 18, 1996 Printed in USA

NDC 0005-3254-32

Selegiline Hydrochloride
Tablets, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg

Usual Adult Dosage
two tablets daily

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 0005-3254-32 1

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51045-96 PRD3

NDC 0005-3254-38

Selegiline Hydrochloride
Tablets, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

30 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg

Usual Adult Dosage
two tablets daily

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 0005-3254-38 3

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51044-96 PRD3

NDC 0005-3254-42

Selegiline Hydrochloride
Tablets, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

90 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg

Usual Adult Dosage
two tablets daily

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 0005-3254-42 0

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51046-96 PRD3

NDC 0005-3254-43

Selegiline Hydrochloride
Tablets, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg

Usual Adult Dosage
two tablets daily

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 0005-3254-43 7

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51048-96 PRD3

NDC 0005-3254-23

Selegiline Hydrochloride

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription

100 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg.

Usual Adult Dosage: two tablets daily.

Store at controlled room temperature 15 -30°C (59°-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

AUG 2 1995

N 3 0005-3254-23 9

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51049-96 PRD3

NDC 0005-3254-48

Selegiline Hydrochloride

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription

120 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg.

Usual Adult Dosage: two tablets daily.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 0005-3254-48 2

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51047-96 PRD3

NDC 0005-3254-31

Selegiline Hydrochloride

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription

500 TABLETS

STANDARD PRODUCTS

Each tablet contains selegiline hydrochloride 5 mg.

Usual Adult Dosage: two tablets daily.

Store at controlled room temperature 15 -30°C (59°-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

N 3 0005-3254-31 4

Control No.

Exp. Date

LEDERLE LABORATORIES
A Division of
American Cyanamid
Company
Pearl River, NY 10965

51050-96 PRD3

NDC 0005-3254-34

Selegiline Hydrochloride

Tablets, USP

5 mg

Each tablet contains selegiline hydrochloride 5 mg.

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

STANDARD PRODUCTS

Usual Adult Dosage: two tablets daily.

Store at controlled room temperature 15 -30°C (59 -86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

LEDERLE LABORATORIES
A Division of
American Cyanamid Company
Pearl River, NY 10965

51051-96 PRD3

N 3 0005-3254-34 5

Control No.

Exp. Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074641

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.3

2. ANDA # 74-641

3. NAME AND ADDRESS OF APPLICANT
Lederle Laboratories
Division of American Cyanamid Co.
Attention: Nicholas C. Tantillo
401 N. Middletown Road
Pearl River, NY 10965-1299

4. BASIS FOR SUBMISSION:

The applicant includes patent and exclusivity information on pages 004-009. The drug is covered by an Orphan Drug Exclusivity which will expire on June 5, 1996.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
Eldepryl Tablets

7. NONPROPRIETARY NAME
Selegiline Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	March 3, 1995
Acknowledgement letter	April 5, 1995
FDA Deficiency Letter	August 7, 1995
Amendment Letter	September 14, 1995
FDA Deficiency Letter	April 5, 1996
Amendment Response	April 15, 1996
Labeling Amendment	April 30, 1996

10. PHARMACOLOGICAL CATEGORY
Antiparkinsonian

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
(-)-R-N, - alpha-dimethy-N-2-propynl phenethylamine hydrochloride

16. RECORDS AND REPORTS
NA

17. COMMENTS
All chemistry deficiencies have been resolved satisfactorily.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
May 3, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074641

BIOEQUIVALENCE REVIEW(S)

JUL 26 1996

Selegiline Hydrochloride
5 mg tablet
ANDA#: 74-641
Reviewer: Gur J.P. Singh
File: 74641O.496

Lederle Laboratories
Pearl River, NY
Submitted:
April 4 and 15, 1996

An Addendum to the Review of Fasting Bioequivalence Study

On 2/2/95 the sponsor submitted fasting and fed bioequivalence studies for its test product selegiline hydrochloride 5 mg tablets. The submission was reviewed (file date: 9/27/95, reviewer: Dr. J Henderson) and found incomplete. On 10/6/95 and 11/20/95, the sponsor submitted two study amendments. The amendments were reviewed (file date 3/11/96) and the responses to deficiency comments #4 and #8 were found incomplete. The sponsor made another amendment on April 4, 1996 which was also reviewed by Dr. J. Henderson. Based on that review the sponsor has submitted satisfactory responses to deficiencies in analytical method validation. Furthermore the reviewer found both fasting and fed studies, and dissolution acceptable. The statistical data supporting the approval of these studies is given in Dr. Henderson's review of September 27, 1995. Based on these data the 90% confidence intervals (CI) for AUC_{0-t}, AUC_{inf} and C_{max} of desmethyl-selegiline, amphetamine and meth-amphetamine were in the acceptable range of 80-125%. On the other hand, the 90% CI for selegiline AUC_{0-t}, AUC_{inf} and C_{max} were outside the acceptable range of 80-125%.

The Division of Bioequivalence has recently revised criteria to document bioequivalence of selegiline tablets under fasting conditions. The criteria to meet bioequivalence requirements under fasting conditions are as follows::

i. 90% CI within 80-125% on log-transformed data for AUC_{0-t}, AUC_{inf} and C_{max} values of desmethyl-selegiline, amphetamine and meth-amphetamine.

ii. Geometric means for AUC_{0-t}, AUC_{inf} and C_{max} values of the test product to be within 80-125% of the respective values of the reference product.

The reviewer has evaluated the fasting study data to determine the status of this study in view of the criterion ii listed above. Based on reviewer's calculations, the test and reference products geometric means are given in table 1 (attached).

Comments:

1 Based on Dr. Henderson's review, the 90% confidence intervals for desmethyl-selegiline, amphetamine and meth-amphetamine were within the acceptable limit of 80-125%.

2. The geometric means of the test product for AUC_{0-t}, AUC_{inf} and C_{max} are within 80-125% of the those of the reference product.

3. Based on above observations, the fasting study performed by Lederle Laboratories on its selegiline hydrochloride is acceptable.

RECOMMENDATIONS:

1. The bioequivalence study (fasting conditions) conducted by Lederle Laboratories on its selegiline hydrochloride 5 mg tablet, lot #93245-0100, comparing it to Eldepryl® 5 mg tablet, lot #3A004B, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Lederle's selegiline hydrochloride 5 mg tablet is bioequivalent under fasting conditions to the reference product Eldepryl® 5 mg tablet manufactured by Somerset.

2. The bioequivalence study (fed conditions) conducted by Lederle Laboratories on its selegiline hydrochloride 5 mg tablet, lot #93245-0100, comparing it to Eldepryl® 5 mg tablet, lot #3A004B, has been previously found acceptable by the Division of Bioequivalence. The study demonstrates that Lederle's selegiline hydrochloride 5 mg tablet is bioequivalent under fed conditions to the reference product Eldepryl® 5 mg tablet manufactured by Somerset.

3. The dissolution testing conducted by Lederle on its selegiline hydrochloride 5 mg tablet, lot #93245-0100, has been previously found acceptable. Dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37° using USP 23 apparatus I (basket) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

From the bioequivalence stand point, the sponsor has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR for 7/26/96

Concur: _____ Date 7/26/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

GJPS 7/25/96/ 74641O.496
cc: ANDA #74-641 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Nerurkar, Singh), Drug File, Division File

Table 1. Selegiline PK-parameter data. ANDA #74-641, Fasting Study (Lederle).
Subject #2,7,11, 15, 24 and 30 deleted because of unacceptable Cmax values.

	Test			REF		
SUBJ	AUC0-t	AUCinf	Cmax	AUC0-t	AUCinf	Cmax
1						
3						
4						
5						
6						
8						
9						
10						
13						
14						
16						
17						
18						
19						
20						
21						
22						
23						
25						
26						
27						
28						
29						
31						
GeoMean	917.61	1251.72	1218.44	751.61	1100.30	1021.56
ArithMean	2233.32	2635.52	2238.83	1908.30	2430.72	1849.68

	Test / Ref		
	AUC0-t	AUCinf	Cmax
GeoMean	**1.22**	**1.14**	**1.19**

SEP 27 1995

Selegiline Hydrochloride
5 mg tablet
ANDA#: 74-641
Reviewer: James D. Henderson
File: 74641SD.295

Lederle Laboratories
Pearl River, NY
Submitted:
February 2, 1995

REVIEW OF FASTING AND FED BIOEQUIVALENCE STUDIES

Background

1. On 2/1/94 the sponsor submitted an inquiry to the DBE (CD BIO-94-94) regarding bioequivalence requirements for generic selegiline hydrochloride products. The two questions posed by the sponsor were answered (JHenderson, letter date 3/25/94) as follows:

- An acceptable limited food study would be required as a condition of approval. The standardized DBE meal should not be used since it contains cheese. Instead, the meal composition used by the DOB for food studies should be employed.

- The measurement of plasma selegiline concentrations should be attempted and the results reported, but pivotal criteria will be applied only to the three metabolites.

2. On 6/13/94 the sponsor submitted protocols for fasting (P-94-055) and fed (P-94-056) bioequivalence studies of its test product selegiline hydrochloride 5 mg tablets. The protocols were found acceptable by the Division with minor modifications (SPShrivastava, file date 8/26/94).

FASTING STUDY

I. Study Site

Clinical and Analytical Site:

Medical Director:
Scientific Director:
Protocol: #940400, 9/23/94
incorporated changes requested by IRB, 10/12/94
amended, 12/12/94
Study: #S446A-5
IRB Approval: 9/27/94
Dosing Dates: Period 1, 10/29/94; Period 2, 11/12/94
Analytical Director:
Analysis Dates: 12/5-1/20/95 (frozen storage

II. Study Design

This study was a randomized, single dose, two-way crossover design in 30 healthy adult male volunteers under fasting conditions with a two week washout. Bioavailability of the sponsor's test product selegiline hydrochloride 5 mg tablets was compared to the reference listed drug (RLD) Eldepryl® 5 mg tablets (Somerset, NDA #19-334, 6/5/89) following a 10 mg dose. Plasma concentrations of the parent drug selegiline and its metabolites desmethylselegiline (DES), amphetamine (A), and methamphetamine (MA) were measured.

III. Subject Selection

Thirty-two healthy, nonsmoking, adult male volunteers (30 subjects plus 2 alternates) were enrolled according to the criteria below. Samples from the first 30 subjects (15 per sequence) were to be analyzed per protocol, with samples from alternates analyzed only if dropouts occurred.

A. inclusion criteria

- male, 18-40 years old
- weight at least 60 kg and within 10% of ideal weight (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983)
- good health as determined from medical history, physical examination, and laboratory tests (hematology, serum chemistry, urinalysis, HIV test)

B. exclusion criteria

- history or presence of significant systemic, organ, or psychiatric disease, including peptic ulcer, extrapyramidal disorders, severe psychosis or profound dementia
- alcoholism or drug abuse within the last year
- hypersensitivity or idiosyncratic reaction to amphetamines, selegiline, or any other MAO inhibitor
- abnormal diet in the last four weeks before study start
- donation of > 500 mL blood in 14 days, 750 mL/3 months, 1000 mL/6 months, 1500 mL/9 months, or 2000 mL/1 year through study completion
- participation in another clinical trial within 28 days of study start
- use of tobacco or marijuana cigarettes, nicotine patches or gum within the last year

IV. Study Procedures

A. treatments

After an overnight fast, subjects received one of the following treatments administered with 180 mL of water:

1) Trt. A (test), selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle lot #93245-0100; potency, 98.8%; theoretical batch size,
manufactured 8/31-9/9/94

2) Trt. B (ref.), Eldepryl® 10 mg (2 X 5 mg tablet), Somerset Lot #3A004B (exp 9/95); potency, 98.8%

After a 14-day washout, subjects were crossed over to the alternate treatment.

B. restrictions

Subjects were confined at the clinical site from 12 hours predose until after the 36-hr draw, and returned for the 48- and 72-hr draws. All medications (including OTC) were prohibited for the 14 days preceding the study. Consumption of alcohol and xanthine-containing foods and beverages was prohibited for 48 hours predose and during sample collection periods. Consumption of foods rich in tyramine was prohibited for 24 hours predose and for 36 hours postdose in each period. Subjects remained seated for the first 2 hours postdose, and then resumed normal activity, avoiding both vigorous exertion and complete rest.

C. blood sampling

Blood samples were collected into EDTA-Vacutainers at 0 (predose), 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. Plasma selegiline and DES levels were determined at 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, and 8 hours postdose (see Results, Protocol Deviations below). Plasma A and MA levels were determined at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. Samples up to and including the 4-hr draw were taken via an indwelling heparin lock. Blood samples were chilled in an ice bath and centrifuged under refrigeration as soon as possible after collection. Plasma was separated, divided into aliquots, and stored frozen at -22 ± 10° pending assay.

D. monitoring

Sitting BP and heart rate were measured predose and within 10 minutes prior to blood draws at 1, 2, 4, and 8 hours postdose.

E. foods and fluids

Subjects fasted overnight and for 4 hours postdose at which time a standardized meal schedule began. Water was not permitted from

2 hours predose until 4 hours postdose but was allowed freely at other times.

V. Data Analysis

A. Analytical Methodology

C. Statistical Analysis

Analysis of variance (ANOVA) was performed on the parameters above using the SAS v. 6.04 GLM procedure with a model containing factors for sequence, subjects nested within sequence, period, and treatment. Significance of the sequence effect was tested against subjects within sequence as the error term. In accordance with the Two One-Sided Tests Procedure, 90% confidence intervals (CI) were calculated for the differences between least squares means (LSM) for AUC and CMAX using both untransformed and log-transformed data.

VII. Results

A. Product Information

1. Formulation:

Test product formulation is shown in Table 1.

2. Dissolution:

Results are shown in Table 2. The dissolution testing is acceptable according to conditions and specifications stated in PF 1994;20:8416.

3. Potency:

Potencies of the biostudy lots were within ± 5%.

4. Batch Size:

Theoretical and finished batch sizes were tablets, respectively (red v. B1.3, p. 4971, 5013).

B. Clinical

1. Completion:

Of the 32 subjects enrolled, 31 subjects completed the study. Subject 12 was withdrawn from the study for medical reasons (viral prodromal symptoms) prior to Period 2, and was replaced by S31.

2. Protocol Deviations:

a. sampling and analysis times

- The original protocol stated that the expected t½ for DES was about 1.3 hr. Subsequent work indicated a longer t½ may occur, and DES was analyzed at both 12 and 16 hours. Selegiline was also analyzed at 12 and 16 hours since it was

assayed along with DES.

- In 26 cases (Trt. A, 9; Trt. B, 17), blood samples were collected at times greater than within two minutes of the scheduled time. Times of sample collection that differed by more than two minutes from the scheduled sampling time were adjusted in the data set to reflect the actual sampling time for PK and statistical analysis.

- Period 1 for subjects 1-4 was analyzed in a single run. Period 2 for subjects 1 and 2 was analyzed within a separate run. Period 2 for subjects 3 and 4 was analyzed within another separate run.

b. missing samples

S17, 0.67 hr sample in Period 1, was not obtained. It is noted in the Clinical Raw Data section (p. 721) that there was "no blood due to difficulty with catheter".

c. inclusion/exclusion criteria

S11 was enrolled after reporting marijuana use within the last 10 months (instead of 12 months per protocol). The Case Report Form (p. 975) indicates that S11 "was accepted into study in error". The reviewer proceeded with S11 included in the data set.

d. restrictions

Four violations of the prohibition from xanthine-containing substances were reported. The reviewer concurs that these events are unlikely to affect the study outcome.

3. Adverse Events

a. Trt. A (test)

There were 8 events involving 7 subjects. All events were judged as not serious and of mild intensity. No treatment was required in any case. Four events were judged as probably or definitely related to the drug or procedure: dizziness (2), headache (1), fainting during draw (1). One event (sleepiness) was judged as possibly related to the drug or procedure. Three events were judged as having other causality.

b. Trt. B (ref.)

There were 5 events involving 4 subjects. All events were judged as not serious and of mild intensity. No treatment was required in any case. One event (headache) was judged as probably related to the drug or procedure. Three events were judged as having other causality.

C. Pharmacokinetics/Statistics

1. plasma concentrations

Mean reported plasma concentrations of selegiline, DES, A, and MA for the test product and the RLD for all 30 subjects completing the study are shown in Tables 3A-D.

a. nonzero predose concentrations

For selegiline, S27 (Period 1, Trt. B) had a determined concentration of 142.1 pg/mL (Raw Data, curve CSZ83, p. 2483), which was 289% of the lowest standard response. For amphetamine, S6 (Period 1, Trt. B) had a determined concentration of 0.472 ng/mL (Raw Data, curve CWY74, p. 2321), which was 205% of the lowest standard response. In both cases, the sponsor set the reported concentration to zero since the study drug had not yet been taken, and since insufficient volume remained for reassay.

b. CMAX as first nonzero concentration

For selegiline, there were seven instances where the first nonzero concentration was the CMAX: Trt. A, Subjects 11, 15; Trt. B, Subjects 2, 7, 15, 24, and 30. However, since pivotal statistical criteria are not applied to the parent drug, the reviewer used the results from all subjects completing the study. For the metabolites, DES, A, and MA, this consideration for CMAX does not apply since the inability to predict metabolite appearance may preclude selection of optimal sampling times.

2. pharmacokinetic parameters

Mean reported pharmacokinetic parameters for the test product and the RLD for all 30 subjects completing the study are shown in Table 4. Statistically significant effects occurred as follows:

- selegiline: period ($p < 0.05$) for logAUC0-t and logAUCINF; treatment ($p < 0.05$) for logAUC0-t and logCMAX
- DES: period ($p < 0.05$) for AUC0-t, AUCINF, logAUC0-t, and logAUCINF; treatment ($p < 0.05$) for AUC0-t, AUCINF, CMAX, logAUC0-t, logAUCINF, and logCMAX

3. test/RLD ratios are shown in Tables 5A-C.

C. Analytical

1. endogenous interferences

Predose samples containing IS were assayed for interferences or contaminants. If a response at the analyte retention time (RT)

is < 20% of the lowest standard response, the interference is considered insignificant. Significant interferences occurred as follows:

- Selegiline: 4 predose samples contained responses of 22.7-96.3% of the lowest standard
- DES: 6 predose samples contained responses of 24.9-96.3% of the lowest standard
- A: 7 predose samples contained responses of 20.1-77.7% of the lowest standard
- MA: 5 predose samples contained responses of 22.3-27.8% of the lowest standard

No significant interferences were observed at the IS retention time in a separate run using extracted subject samples (near CMAX values) in absence of IS.

2. during study validation: Table 6

3. prestudy validation: Table 7

4. S8 samples were analyzed in two separate runs for amphetamine but both runs failed to meet acceptance criteria.

VIII.Comments (Fasting Study)

1. Using the data on diskette supplied by the sponsor (Table 8, Condition 2), the reviewer performed ANOVA with the GLM procedure of SAS and confirmed the 90% CI results reported by the sponsor (Table 8, Condition 1) for log-transformed AUC0-t, AUCINF, and CMAX for the three metabolites (DES, A, and MA).

2. In two cases (selegiline, S27, Trt. B, and amphetamine, S6, Trt. B), there were nonzero predose levels at the start of Period 1. For the pivotal metabolite A, the worst case scenario would be a contaminant present at a constant concentration throughout the sampling. However, samples at 36, 48, and 72 hr had determined concentrations of 0.425 and 0.288 ng/mL and BLQ, respectively, arguing against the presence of a contaminant.

For S6, Period 1, Trt. B, it is noted from the raw data that initial determined concentrations of 1.096, 0.486, and 1.772 ng/mL occurred at 0.5, 1, and 2 hr, respectively. All these samples, as well as the predose sample, were suspected outliers (see Reassays below).

3. In general, the λ_z values were acceptable, with only 3 cases for DES and 1 case for A where $R^2 < 0.9$. For selegiline, the sponsor could not estimate λ_z in 16 of 60 cases; however, this analyte is not pivotal for this study.

4. The sponsor reported values for the AUC0-t/AUCINF ratio, but

did not report values for duration of sampling (TLAST/t½) or washout (336/t½).

5. For each reported analytical run and for each of the three metabolites, at least 4/6 QC samples had determined values within the sponsor's allowable ranges (± 20% for Low QC, ± 15% for Middle QC, ± 10% for High QC), with at least one QC from each level acceptable.

6. For selegiline, DES, and MA, calibration curves consisted of eight standards; at least 6 of the standard samples had determined back-calculated values within ± 20% of nominal for standard concentrations < Low QC, and within ± 15% of nominal for standard concentrations > Low QC (except DES curve CSZ83 with 5 of 8). The amphetamine calibration curves consisted of seven standards; at least 5 of the standard samples met the same criteria.

7. Reassays and Adjustments to Data Sets:

- **DES**: According to Table T6.2, a total of 66 DES samples (5.5% of total number of DES samples) were reassayed: lost in processing, 23; poor chromatography, 1; suspected outlier, 5; outside range, 37. Although the sponsor's organization of data makes sample tracking difficult, it appears that these 66 samples were reassayed on curves CSZ86 (p. 2526) or CSZ91 (p. 2532), and that the reassay value was reported. The sponsor states that some postdose plasma concentrations could not be reported (meaning, apparently, after attempted reassay), and were set to "missing" for PK and statistical analysis. These 12 samples were reported as "R" in the Subject/Data tables: lost in processing, 4; suspected outlier, 2; outside range, 6.

  Four of the values reported as "R" were for S16, Per. 2, Trt. A, at 1, 1.167, 1.33, and 1,5 hr (TMAX 1.75 hr). Three values were reported as "R" for S16, Per. 1, Trt. B, at 0.5, 0.67, and 0.833 hr (TMAX 1 .0 hr).

- **A**: According to Table T5.3, a total of 22 A samples (2.7% of total number of A samples) were reassayed: lost in processing, 15; suspected outlier, 5; high/low standard missing, 2. These 22 samples were reassayed on curves CWY94 (p. 2540) or CWY95 (p. 2545), and the reassay value was reported. The sponsor states that some postdose plasma concentrations could not be reported (meaning, apparently, after attempted reassay), and were set to missing for PK and statistical analysis. These 21 samples were reported as "R" in the Subject/Data tables: lost in processing, 15; suspected outlier, 4; high/low standard missing., 2.

  Six of the values reported as "R" were for S27, Per. 2, Trt.

A, at 0.5, 2, 4, 36, 48, and 72 hr (TMAX 8 hr). Three values were reported as "R" for S27, Per. 1, Trt. B, at 36, 48, and 72. Four of the values reported as "R" were for S6, Per. 1, Trt. B, at 0.5, 1, 2, and 6 hr (TMAX 8 hr).

- **MA**: According to Table T6.4, a total of 5 MA samples were reassayed: lost in processing, 1; suspected outlier, 4. Three samples were reported as "R": lost in processing, 1; suspected outlier, 2.

The reviewer repeated the SAS GLM analysis after excluding the following data sets: DES, S16; A, S6 and S27. The results are shown in Table 8, Condition 3.

8. Suspected PK outliers:

- **DES**: Five samples were originally coded as suspected outliers: 16-0-1, 18-5-1, 23-12-1, 27-6-1, and 8-1.167-2. Two of these were reported as "R" (23-12-1 and 27-6-1) for reasons not apparent to the reviewer. For example, the duplicate reassays for sample 23-12-1 are shown in the Raw Data for curve CSZ91 (p. 2533, injections #48 and 25) with calculated values of BLQ. However, these injections are coded "B" (lost in processing), and the sponsor does not explain how samples lost in processing can have determined values of BLQ. The reviewer could not locate the reassays for sample 27-6-1.

  The remaining three samples were reassayed in duplicate and the results shown in Table T5.2, p. 1208. In all three cases, the median value was reported and the median value was one of the reassay values.

- **A**: Five samples were originally coded as suspected outliers (Table T5.3, p. 1215): 6-0-1, 6-0.5-1, 6-1-1, 6-2-1, and 6-6-1. The reviewer could not locate any reassay values for these samples. Predose sample 6-0-1 (discussed above, Comment #2) was reported as BLQ, and the other four were reported as "R". As shown in Table 8, Condition 3, the reviewer performed additional data analysis with S6 excluded.

- **MA**: Four samples were originally coded as suspected outliers (Table T6.4, p. 1217): 6-2-1, 6-6-1, 8-2-1, and 31-72-2. Two of these (6-6-1 and 31-72-2) were reported as "R". In two cases (6-2-1 and 8-2-1, the median value was reported and the median value was one of the reassay values.

9. The absolute recovery data from the prestudy validation (Table 7) was generated from QC samples. It was not explained how the determined values for the QC samples represent recovery after sample extraction and processing, given that these

determined values are used to indicate assay accuracy. Typically, absolute recovery is based on comparison of peak heights or areas of extracted/processed samples compared to unextracted solutions. Recovery of the IS is designated as % deviation, presumably from the nominal concentration.

10. The sponsor provided chromatograms from Subjects 5, 9, 10, 13, 14, and 16. For each subject, there were two sets of chromatograms: curves for selegiline and DES, and CTA curves for A and MA (renamed in raw data tables). Each set consisted of three reference injections (start, middle, and end of run); a blank not containing any analyte or IS; predose samples from both periods containing only IS; standard A, 0 ng/mL of analyte with IS, start and repeated at end of run; standards B-I; QC samples; subject samples from both periods. The chromatograms were presented with scales for both retention time (RT) and scan number, but the sponsor chose to identify peaks by scan number.

- Blanks: Of the 12 blank samples submitted, at least five showed traces of the IS peak.

- Predose samples: Of the 24 predose samples submitted, at least 13 showed traces of one of the analytes (a peak identified by scan number at the scan number position of one of the analytes). In one case (S16, Per. 1), the chromatogram (p. 2127) appears to be a subject sample or a reference sample with large peaks for selegiline, IS, and DES.

- STD A samples: Of the 24 STD A samples submitted, at least 11 showed traces of one of the analytes.

- Between 8 to 22 samples were labeled "chromatogram not used" for both analytes in each run. It appears that this occurred in cases where the analytical results were not intended to be used for the analyte at that specific sampling time. For example, samples 5,48,1 (Subject 5, Per. 1, 48-hr), p. 1441, and 9,48,1, p. 1581 are marked "chromatogram not used" for both selegiline and DES since results were not considered beyond 16 hours for these analytes. Another example is from curve CTA47 on p. 1498, where all three chromatograms (MA, IS, and A) are marked "chromatogram not used" for sample 5,5.0,2. However, results for MA and A were not reported at 5 hours.

FED STUDY

I. Study Site

Clinical and Analytical Site:

Medical Director:
Scientific Director:
Protocol: #940401, original 9/23/94
final, 10/7/94
amended, 12/12/94
IRB Approval: 9/27/94
Dosing Dates: Period 1, 10/8/94 (all subjects)
Period 2, 10/22/94 (S1-6, 8-9, 11, 15-19, 21)
Period 2, 11/5/94 (S12-14, 20)
Period 3, 11/5/94 (S1-6, 8-9, 11, 15-19, 21)
Analytical Director:
Analysis Dates: 12/12/94-2/5/95 (frozen storage

II. Study Design

This study was a randomized, single dose, three-way crossover design (three treatments and periods, six sequences) in 21 healthy adult male volunteers with a two week washout. Bioavailability of the sponsor's test product selegiline hydrochloride 5 mg tablets was compared to the reference listed drug (RLD) Eldepryl® 5 mg tablets (Somerset, NDA #19-334, 6/5/89) following a 10 mg dose under the following conditions: test product and RLD after a standard breakfast; and, test product under fed and fasting conditions. Plasma concentrations of the parent drug selegiline and its metabolites desmethylselegiline (DES), amphetamine (A), and methamphetamine (MA) were measured.

III. Subject Selection

Twenty-one healthy adult male nonsmoking subjects were enrolled into the study according to the same criteria as used in the fasting study. Dropouts were not replaced as per protocol.

IV. Study Procedures

A. treatments

After an overnight fast, subjects received one of the following treatments administered with 180 mL of water:

1) Trt. A (test), selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle lot #93245-0100, fasted

2) Trt. B (test), selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle lot #93245-0100, fed

2) Trt. C (ref.), Eldepryl® 10 mg (2 X 5 mg tablet), Somerset Lot #3A004B (exp 9/95), fed

After 14-day washout periods, subjects were crossed over to the alternate treatments in Periods 2 and 3. For Subjects 12, 13, 14, and 20, the washout period between Periods 1 and 2 was 28 days.

B. restrictions

Subjects were confined at the clinical site from 12 hours predose until after the 36-hr draw, and returned for the 48- and 72-hr draws. All medications (including OTC) were prohibited for the 14 days preceding the study. Consumption of alcohol and xanthine-containing foods and beverages was prohibited for 48 hours predose and during sample collection periods. Consumption of foods rich in tyramine was prohibited for 24 hours predose and for 36 hours postdose in each period. Subjects remained seated for the first 2 hours postdose, and then resumed normal activity, avoiding both vigorous exertion and complete rest.

C. blood sampling

Blood samples were collected into EDTA-Vacutainers at 0 (predose), 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. Plasma selegiline and DES levels were determined at 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, and 8 hours postdose (see Results, Protocol Deviations below). Plasma A and MA levels were determined at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. Samples up to and including the 4-hr draw were taken via an indwelling heparin lock. Blood samples were chilled in an ice bath and centrifuged under refigeration as soon as possible after collection. Plasma was separated, divided into aliquots, and stored frozen at -22 ± 10° pending assay.

D. monitoring

Sitting BP and heart rate were measured predose and within 10 minutes prior to blood draws at 1, 2, 4, and 8 hours postdose.

E. foods and fluids

Subjects were given a standard meal and snack the evening prior to dosing. Water was not permitted from 2 hours predose until 4 hours postdose but was allowed freely at other times.

Trt. A: Subjects fasted overnight and for 4 hours postdose at which time a standardized meal schedule began. Although the meal plans were to be identical for all periods, subjects did receive different main courses for the 4-hour postdose meal in Period 1

compared to Periods 2 and 3. In addition, although the protocol specified that tyramine-rich foods would be prohibited from 24 hours before until 36 hours after dosing, subjects were served a cheese-containing 4-hr postdose meal in Period 1.

Trts. B and C: After a supervised overnight fast and 30 minutes before scheduled dosing times, subjects received a standard breakfast consisting of two eggs fried in butter, two slices of bacon, two slices of toasted white bread spread with butter, two ounces of hash brown potatoes, and 240 mL of whole milk. Four hours postdose, a standardized meal schedule began.

V. Data Analysis

A. Analytical Methodology

B. Data Analysis

Pharmacokinetic parameters for selegiline, DES, A and MA were calculated in the same manner as in the fasting study.

C. Statistical Analysis

Data from only those subjects who completed at least two periods of the study was submitted for statistical analysis. Analysis of variance (ANOVA) was performed on the parameters above using the SAS v. 6.04 GLM procedure with a model containing factors for subjects, period, treatment, and first-order carryover. Ratio analysis was performed using the least squares means (LSM) for AUC and CMAX using both untransformed and log-transformed data.

VII. Results

A. Product Information: same as for fasting study

B. Clinical

1. Completion:

Of the 21 subjects enrolled, 13 subjects completed all three phases of the study, and 19 subjects completed at least two periods of the study.

- S10 withdrew for personal reasons after the 3-hr draw in Period 1.
- S7 was withdrawn prior to Period 2 dosing due to abnormal

hematology results per protocol.

- S17 withdrew for personal reasons 3 days after Period 2 dosing.
- Subjects 6, 12, 13, 14, and 20 were withdrawn from the study prior to Period 3 due to low results from hematology tests per protocol.

2. Protocol Deviations:

a. sampling and analysis times

- The original protocol stated that the expected t½ for DES was about 1.3 hr. Subsequent work indicated a longer t½ may occur, and DES was analyzed at both 12 and 16 hours. Selegiline was also analyzed at 12 and 16 hours since it was assayed along with DES.

- In 37 cases (Trt. A, 11; Trt. B, 13; Trt. C, 13), blood samples were collected at times greater than within two minutes of the scheduled time. Times of sample collection that differed by more than two minutes from the scheduled sampling time were adjusted in the data set to reflect the actual sampling time for PK and statistical analysis.

b. consumption of high-fat breakfast

All subjects completed the high-fat breakfast except S13 who did not consume 18 g of hash brown potatoes.

c. inclusion/exclusion criteria

S12 was enrolled in violation of weight restrictions (0.5 kg below the lower limit of his ideal weight range) at screening. When reweighed at Period 1 check-in, S12 was within the weight limits specified in the protocol. S12 completed only the first two periods of the study.

d. restrictions

S11 took Polysporin® (topical antibiotic) in response to a medical event judged to be unrelated to the study or procedure. The reviewer concurs that this is unlikely to affect the study outcome.

3. Adverse Events

a. Trt. A (test, fasted)

There were 6 events involving 4 subjects. All events were judged as not serious and of mild intensity. Treatment was required in one case (S13, Trt. A, ice applied to venipuncture site). Four events were judged as definitely related to the venipuncture

sampling procedure. Two events were judged as having other causality.

b. Trt. B (test fed)

There were 24 events involving 10 subjects. All events were judged as not serious and of mild intensity except for S11, foot laceration, and S17, pain, faintness, vomiting, and edema due to fall and elbow injury, all of moderate intensity. Treatment was required in the following cases: S1, cold compress for headache and hot flashes; S1, hot water bag applied to venipuncture site; S17, sling and ice application to elbow. Eleven events were judged as due to the drug administration: headache (3), dizziness (1), hot flashes (1), sweating (1), numbness in fingers (1), nausea (1), loose stools (1), vomiting (1), stomach pain (1). Seven events was judged as due to the procedure. Six events were judged as having other causality.

c. Trt. C (reference fed)

There were 8 events involving 6 subjects. All events were judged as not serious and of mild intensity, and no treatment was required. None of the events were judged as due to the drug.

C. Pharmacokinetics/Statistics

1. <u>plasma concentrations</u>

Mean reported plasma concentrations of selegiline, DES, A, and MA for the test product and the RLD for the 19 subjects completing at least two phases of the study are shown in Tables 9A-D.

a. predose samples

The sponsor did not report predose concentrations for: S16, A, Per. 3; S16, MA, Per. 2; and, S16, MA, Per. 3. In all three cases, the sponsor set the reported concentration to zero since: 1) there was a 14-day washout between dosings; 2) the t½ for A in Period 2 for this subject was 13.65 hr (24.6 half-lives); 3) the t½ for MA in Periods 1 and 2 for this subject were 9.64 hr (34.8 half-lives) and 14.89 hr (22.6 half-lives), respectively.

On p. 3539 of the Analytical Report, the sponsor states that subject sample 16-0-2 for methamphetamine contained interference of 166% (of the lowest standard), and that insufficient volume of plasma remained for reanalysis. On p. 4690 (Raw data tables), the calculated nonzero predose concentration is listed as 0.738 ng/mL as obtained from the standard curve results.

On p. 4688, sample 16-0-3 for A is listed as "No peak" for A and IS with the explanation "lost in processing". On p. 4690, sample 16-0-3 for MA is listed as "No peak" for A and IS with the

explanation "lost in processing". Apparently, these samples were not reassayed.

b. CMAX as first nonzero concentration

For selegiline, there was one instance (Trt. A, S1) where the first nonzero concentration was the CMAX. However, pivotal statistical criteria are not applied to the parent drug. For the metabolites, DES, A, and MA, this consideration for CMAX does not apply since the inability to predict metabolite appearance may preclude selection of optimal sampling times.

2. pharmacokinetic parameters

Mean reported pharmacokinetic parameters for the test product and the RLD for the 19 subjects completing at least two periods of the study are shown in Table 10. The sponsor used a statistical model containing terms for SUBJECT, PERIOD, TREATMENT, RESIDA, and RESIDB, where the last two terms are construct variables whose values (1, 0, -1) in Periods 2 and 3 depend on the treatment in the preceding period and whose value is 0 in Period 1. Statistically significant effects occurred as follows:

- selegiline: period ($p < 0.05$) for AUC0-t, logAUC0-t, logAUCINF, and logCMAX
- DES: period ($p < 0.05$) for AUC0-t, AUCINF, logAUC0-t, and logAUCINF; resida ($p < 0.1$) for logCMAX; residb ($p < 0.1$) for logAUC0-t and logAUCINF
- A: period ($p < 0.05$) for AUC0-t, AUCINF, logAUC0-t, and logAUCINF
- MA: period ($p < 0.05$) for AUC0-t, AUCINF, CMAX, logAUC0-t, and logAUCINF; residb ($p < 0.1$) for CMAX and logCMAX

Reported least squares means (LSM) and ratios (B/C) are shown in Table 11 and Table 12 (Condition 1).

C. Analytical

1. endogenous interferences

Predose samples containing IS were assayed for interferences or contaminants. If a response at the analyte retention time (RT) is < 20% of the lowest standard response, the interference is considered insignificant. Significant interferences occurred as follows (excluding the nonzero predose sample described above):

- Selegiline: 12 predose samples contained responses of 21.8-66.5% of the lowest standard
- DES: 5 predose samples contained responses of 23.0-32.5% of

the lowest standard

- A: 5 predose samples contained responses of 22.3-42.5% of the lowest standard
- MA: 1 predose sample contained a response of 26.7% of the lowest standard

No significant interferences were observed at the IS retention time in a separate run using extracted subject samples (near CMAX values) in absence of IS.

2. during study validation: Table 13

3. prestudy validation: Table 7

4. For S14, amphetamine concentration values could not be reported due to analytical problems (failure to meet acceptance criteria from three separate runs).

VIII. Comments

1. Using the data provided on diskette and the sponsor's statistical model, the reviewer confirmed the values for ratios of geometric means (B/C) reported by the sponsor for the three pivotal metabolites DES, A, and MA (Table 12, Condition 2).

2. Thirteen of the 21 subjects enrolled completed all three phases of the study. Therefore, the reviewer performed ANOVA using the GLM procedure of SAS, and the sponsor's statistical model, on the data set (sponsor's diskette) containing only these 13 subjects (1, 2, 3, 4, 5, 8, 9, 11, 15, 16, 18, 19, 21). The results are shown in Table 12, Condition 3. Statistically significant effects were seen as follows:

- DES: period ($p < 0.05$) for logAUC0-t and logAUCINF; RESIDB ($p < 0.1$) for logAUC0-t and logAUCINF; RESIDA ($p < 0.1$) for logCMAX
- A: period ($p < 0.05$) for logAUC0-t and logAUCINF; RESIDB ($p < 0.1$) for logCMAX
- MA: period ($p < 0.05$) for logAUC0-t and logAUCINF; RESIDB ($p < 0.1$) for logCMAX

3. The reviewer also repeated the data analysis for the 13 subjects completing the study using a first-order residual model containing the terms SEQUENCE, SUBJECT(SEQUENCE), PERIOD, TREATMENT, and RES1. The results are shown in Table 12, Condition 4. Statistically significant effects were seen as follows:

- DES: RES1 ($p < 0.1$) for logCMAX

- A: period ($p < 0.05$) for logAUC0-t and logAUCINF

- MA: period ($p < 0.05$) for logAUC0-t and logAUCINF

Due to the significant residual effect noted for logCMAX (DES), data analysis excluding Treatment A was performed only for A and MA. These results are shown in Table 12, Condition 5. A statistically significant period effect ($p < 0.05$) occurred for logAUCINF (MA).

4. For selegiline, the sponsor could not estimate λ_z values in nine cases. For DES, the reviewer considers λ_z inestimable in two cases: S1 (A) and S16 (B), $R^2 < 0.9$. For A, the reviewer considers λ_z inestimable in three cases: S1 (C), last point bounces up; S5 (A, C), $R^2 < 0.9$. The ANOVA for logAUCINF (DES and A) was repeated with these cases deleted, using the first-order residual model; the results are shown in Table 12, Condition 6.

5. For each reported analytical run and for each of the three metabolites, at least 4/6 QC samples had determined values within the sponsor's allowable ranges (± 20% for Low QC, ± 15% for Middle QC, ± 10% for High QC), with at least one QC from each level acceptable.

6. For selegiline, DES, and MA, calibration curves consisted of eight standards; at least 6 of the standard samples had determined back-calculated values within ± 20% of nominal for standard concentrations < Low QC, and within ± 15% of nominal for standard concentrations > Low QC. The amphetamine calibration curves consisted of seven standards; at least 5 of the standard samples met the same criteria.

7. Reassays and Adjustments to Data Sets:

- **DES**: According to Table T6.2 (p. 3590), a total of 25 DES samples were reassayed: lost in processing, 15; suspected outlier, 6; outside range, 4. Eleven samples were reported as "R" in the Subject/Data tables: lost in processing, 6; suspected outlier, 4; outside range, 1.

  Table T5.2 lists only 5 of the 6 samples reassayed as suspected outliers (sample 5-2-2 is missing). In 3 cases, no final result could be reported. In one case, the median value was reported, and in the remaining case the original value was reported.

- **A**: According to Table T5.3, a total of 20 A samples were reassayed as lost in processing. Twenty samples were reported as "R" in the Subject/Data tables as lost in processing.

Six of the values reported as "R" were for S5, Per. 3, Trt. A, at 0.5, 1, 4, 6, 48, and 72 hr. Five values were reported as "R" for S5, Per. 1, Trt. B, at 0.5, 1, 16, 36, and 72. Four of the values reported as "R" were for S5, Per. 2, Trt. C, at 0.5, 1, 2, and 72 hr.

- **MA**: According to Table T6.4, a total of 21 MA samples were reassayed: lost in processing, 19; suspected outlier, 1; high/low standard missing, 1. Twenty-one samples were reported as "R": lost in processing, 19; suspected outlier, 1; high/low standard missing, 1.

  Three of the values reported as "R" were for S5, Per. 3, Trt. A, at 0.5, 48, and 72 hr. Four of the values reported as "R" were for S5, Per. 1, Trt. B, at 0.5, 16, 36, and 72 hr. Five of the values reported as "R" were for S5, Per. 2, Trt. C, at 0.5, 1, 2, 48, and 72 hr.

Since all the data sets for S5 were incomplete, the reviewer repeated the SAS GLM analysis after excluding S5 from the A and MA data sets. The results are shown in Table 12, Condition 7.

8. The sponsor provided chromatograms from Subjects 1, 4, 9, and 11. For each subject, there were two sets of chromatograms: CXB curves for selegiline and DES, and CXC curves for A and MA. Each set consisted of three reference injections (start, middle, and end of run); a blank not containing any analyte or IS; predose samples from both periods containing only IS; standard A, 0 ng/mL of analyte with IS, start and repeated at end of run; standards B-I; QC samples; subject samples from three periods. The chromatograms were presented with scales for both retention time (RT) and scan number, but the sponsor chose to identify peaks by scan number.

- Blanks: Of the 8 blank samples submitted, at least four samples showed traces of the IS peak, and four samples showed trace peaks for either selegiline or DES.

- Predose samples: Of the 24 predose samples submitted, at least 21 showed traces of one of the analytes (a peak identified by scan number at the scan number position of one of the analytes).

- STD A samples: Of the 18 STD A samples submitted, at least 9 showed traces of one of the analytes.

DEFICIENCIES

Applicable to Both Studies:

1. The sponsor should calculate the following parameters (both mean and individual data) for the three analytes desmethylselegiline, amphetamine, and methamphetamine: a) DURATION of sampling (=TLAST/t½), where TLAST is the time of the last quantifiable concentration); and b) WASHOUT (=336/t½).

2. The sponsor is requested to submit another 3.5" diskette containing the pharmacokinetic data from both studies for the three analytes desmethylselegiline, amphetamine, and methamphetamine, and the data requested above in deficiency #1, in the following format:

SUBJ SEQ PER TRT AUCT AUCINF RATIO CMAX TMAX KEL HALF TLAST DURATION WASHOUT

RATIO is the AUC0-t/AUCINF ratio which was reported but not included in the data on the original diskettes. To facilitate the review process, it is specifically requested that the plasma concentrations be omitted from these data sets.

3. To facilitate sample tracking, the sponsor is requested to provide tables from both studies for the three pivotal metabolites (desmethylselegiline, amphetamine, and methamphetamine) containing entries for <u>all reassayed samples</u> and for <u>all samples reported finally as "R"</u> (not reportable). These tables should contain sample identifications, initial values, initial assay curve, reasons for reassay or why reassay could not be done, reassay curve, reassay values, reported values, and reasons for reported values.

4. In Table T6.2 (fasting study, p. 1212) and Table T6.2 (fed study, p. 3590), it is noted that 37 and 4 desmethylselegiline samples, respectively, were reassayed because they were outside the range of the standard curve. The sponsor should submit complete details of the dilution method used to reassay these samples and the validation data <u>performed at the time of the study</u> (with dates of sample analysis) that supports this method.

5. In the analytical validation, the sponsor reported data for recovery based on determined values of QC samples. Typically, absolute recovery is calculated from ratios of peak height or area counts of extracted/processed samples compared to unextracted aqueous standards. The sponsor must explain how the results from QC samples represent the analyte recovery.

6. The analytical SOP is purged of many details and the studies are considered incomplete until all the missing details are

provided.

7. Please explain why only seven standards were used for the amphetamine assay when the analytical SOP requires eight standards (p. 1236, fasting study, and p. 3610, food study).

8. Please provide the rationale and data used to justify the selection of a quadratic function and a weighting factor of $1/CONC^2$ for standard curves.

Applicable to the Fasting Study:

9. The sponsor should comment on the presence of large peaks for selegiline, internal standard, and desmethylselegiline in the fasting study predose sample for Subject 16, Period 1 (p. 2127).

Applicable to the Food Study:

10. The food study should be reanalyzed using data only from the 13 subjects completing all three study phases.

RECOMMENDATIONS

1. The bioequivalence study (fasting conditions) conducted by Lederle Laboratories on its selegiline hydrochloride 5 mg tablet, lot #93245-0100, comparing it to Eldepryl® 5 mg tablet, lot #3A004B, has been found incomplete by the Division of Bioequivalence due to deficiencies 1-9.

2. The bioequivalence study (fed conditions) conducted by Lederle Laboratories on its selegiline hydrochloride 5 mg tablet, lot #93245-0100, comparing it to Eldepryl® 5 mg tablet, lot #3A004B, has been found incomplete by the Division of Bioequivalence due to deficiencies 1-8 and 10.

3. The sponsor should be informed of deficiency comments 1-10 and recommendations 1-2.

James D. Henderson

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

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Table 1 - Formulation of the Test Product

Ingredient	mg/tablet
citric acid anhydrous, USP	
microcrystalline cellulose, NF	
lactose monohydrate, NF	
magnesium stearate, NF	
selegiline hydrochloride	5.000
purified water, USP	

* used in manufacturing but does not appear in final product

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): selegiline hydrochloride
Dose Strength: 5 mg tablet
ANDA No.: 74-641
Firm: Lederle
Submission Date: 2/2/95
File Name: 74641SD.295

I. Dissolution Testing (PF Method):

PF Nov.-Dec. 1994 Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium: water Volume: 500 mL
Specifications: NLT 20 minutes
Reference Drug: Eldepryl® (Somerset)
Assay Methodology: not stated

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #93245-0100 Strength (mg) 5			Reference Product Lot #3A004B exp 9/95 Strength (mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	98		4.9	90		5.5
10	103		1.1	99		2.8
20	104		0.9	101		2.4
30	104		1.3	101		1.6

Table 3A - Mean Reported Plasma Concentrations of Selegiline (pg/mL, N = 30, Fasting Study)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) CV(%)	% diff.
0	0.00	-	0.00	-	-
0.167	4.82	381	40.56	300	-88.1164
0.33	460.39	176	599.49	206	-23.2031
0.5	1294.49	167	960.86	152	34.72202
0.67	1314.21[1]	194	830.12	140	58.31579
0.833	1236.74	194	807.1[1]	187	53.23066
1	1012.59[1]	184	777.47	237	30.24181
1.167	907.00[1]	203	622.61	258	45.67723
1.33	639.39[1]	185	586.56	253	9.006922
1.5	579.67[1]	184	492.89[1]	267	17.60633
1.75	358.37	194	333.32	235	7.515301
2	283.26	218	249.58	286	13.49467
2.5	152.29[1]	222	166.68	347	-8.63271
3	108.68	271	132.67	343	-18.0825
4	63.84	285	85.62[1]	372	-25.4389
5	43.21	264	37.92	394	13.95042
6	30.12	291	22.2[1]	449	35.61459
8	18.75	322	14.07	548	33.26226
12	7.23	433	7.7	548	-6.1039
16	3.00	548	3.71[1]	538	-19.1593

[1] N = 29

Trt. A = selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle
Trt. B = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset

Table 3B - Mean Reported Plasma Concentrations of Desmethylselegiline (pg/mL, N = 30, Fasting Study)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) CV(%)	% diff.
0	0.00	-	0.00	-	-
0.167	49.53	450	590.91	392	-91.618
0.33	2630.49	106	3679.66[1]	117	-28.5127
0.5	9145.82	74	8353.11[1]	71	9.489985
0.67	11649.8[1]	54	11099.52[1]	48	4.957773
0.833	13369.2	46	11610.99[1]	34	15.14263
1	12417.9[1]	33	11399.66	30	8.932284
1.167	11686.2[1]	34	10635.52	33	9.879066
1.33	10693.2[1]	38	9931.33	36	7.67148
1.5	10431.8[1]	40	8989.16	37	16.04877
1.75	9040.39	43	7807.38	41	15.79288
2	7699.77	48	7081.09	47	8.737073
2.5	5749	47	5220.97	46	10.11364
3	4638.07	57	4218.55	51	9.944649
4	3185.39	60	2926	62	8.865003
5	2180.27	66	1903.94[1]	59	14.51353
6	1697.69	71	1487.01[1]	58	14.16795
8	1159.98	77	1023.73	69	13.30917
12	590.6[1]	98	473.73	90	24.67228
16	330.42	111	293.98[1]	97	12.39502

[1] N = 29

Trt. A = selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle
Trt. B = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset

Table 3C - Plasma Concentrations of Amphetamine (ng/mL, N=29*, Fasting Study)

Time(hr)	Trt. A (mean)	CV(%)	Trt. B (mean)	CV(%)	% diff.
0	0.00	-	0.00	-	-
0.5	0.4489[1]	106	0.4509[3]	107	-0.44796
1	1.5739	53	1.5995[1]	39	-1.60112
2	2.5999[1]	34	2.6154[1]	27	-0.59264
3	2.8045	25	2.7061[1]	25	3.635846
4	2.9105[1]	23	2.8808	28	1.031311
6	3.0275	22	3.0286[1]	23	-0.03665
8	3.1752	21	3.3171	26	-4.27783
12	2.958	22	2.8672	28	3.166853
16	2.3799	24	2.4671	23	-3.53451
24	1.7762	32	1.7271	31	2.842916
36	1.3566[1]	37	1.31[1]	42	3.479024
48	0.7767[2]	49	0.6777[1]	42	14.60949
72	0.2066[3]	96	0.1646[3]	106	25.51175

* S8 was analyzed in two separate runs for amphetamine, but both runs failed to meet acceptance criteria.

[1] N = 28 [2] N = 27 [3] N = 26

Trt. A = selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle
Trt. B = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset

Table 3D - Plasma Concentrations of Methamphetamine (ng/mL, N = 30, Fasting Study)

Time(hr)	Trt. A (mean)	CV(%)	Trt. B (mean)	CV(%)	% diff.
0	0.00	-	0.00	-	-
0.5	2.3706	89	2.5174[4]	126	-5.8329
1	7.4628	47	6.7506	40	10.5502
2	10.4541	22	10.2461	27	2.03004
3	10.4664	18	9.9887	23	4.7824
4	10.3425	17	10.006	21	3.36298
6	9.9929	18	9.493[4]	17	5.26155
8	9.771	21	9.7159	26	0.56711
12	8.0217	22	7.7461	28	3.55792
16	6.1001	28	6.0637	30	0.60029
24	4.0203	36	3.8482	36	4.47222
36	2.6044	47	2.5577	55	1.82586
48	1.2553	52	1.1669	61	7.57563
72	0.2224	149	0.2254[4]	168	-1.3485

[1] N = 28 [2] N = 27 [3] N = 26 [4] N = 29

Trt. A = selegiline hydrochloride 10 mg (2 X 5 mg tablet), Lederle
Trt. B = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset

Table 4 - Mean[1] Reported Pharmacokinetic Parameters for Selegiline, DES, A, and MA (N = 30, Fasting Study)

Parameter	Selegiline	Desmethyl-selegiline	Amphetamine[5]	Meth-amphetamine
AUC0-t	(ph*hr/mL)	(ph*hr/mL)	(ng*hr/mL)	(ng*hr/mL)
Test (A)				
mean	1813.97	39832.7	99.11	251
CV(%)	202	50	31	28
N	30	30	29	30
Ref. (B)				
mean	1539.39	35813	96.31	242.8
CV (%)	245	45	31	32
N	30	30	29	30
% Diff.[2]	17.8	11.2	2.9	3.4
90% CI	88.0-147.7	105.2-117.3	94.7-111.1	95.2-111.5
lnAUC0-t				
ratio[3]	1.361	1.095	1.030	1.044
90% CI	106.6-173.9	104.8-114.4	95.7-110.8	97.1-112.4
AUCINF	(pg*hr/mL)	(pg*hr/mL)	(ng*hr/mL)	(ng*hr/mL)
Test (A)				
mean	2162.51[4]	42549.1	109.89	267
CV(%)	172	52	30	27
N	23	30	29	30
Ref. (B)				
mean	1744.38	38044.1	105.28	258.8
CV(%)	206	47	28	32
N	21	30	28	30
% Diff.	23.9	11.8	4.4	3.2
90% CI	76.8-171.1	105.4-118.2	95.7-113.0	95.4-111.1
lnAUCINF				
ratio	1.207	1.099	1.042	1.043
90% CI	94.4-154.3	105.2-114.8	96.8-112.3	97.2-111.9
CMAX	(pg/mL)	(pg/mL)	(ng/mL)	(ng/mL)
Test (A)				
mean	1861.94	15494.5	3.4486	11.7952
CV(%)	142	31	20	17
N	30	30	29	30
Ref.				
mean	1511.01	14001.4	3.5098	11.4603
CV(%)	143	28	23	25
N	30	30	29	30
% Diff.	23.2	10.7	-1.7	2.9
90% CI	92.5-153.9	103.5-117.8	91.8-104.7	95.1-110.7
lnCMAX				
ratio	1.324	1.097	0.988	1.042
90% CI	105.6-165.9	102.0-118.0	93.2-104.8	97.1-111.8

TMAX	(hr)	(hr)	(hr)	(hr)
Test (A)				
mean	0.769	0.937	7.138	3.7
CV(%)	42	39	48	62
N	30	30	29	30
Ref. (B)				
mean	0.691	0.876	6.586	4.033
CV(%)	43	42	41	59
N	30	30	29	30
% Diff.	11.3	7.0	8.4	-8.2
KEL	(hr^{-1})	(hr^{-1})	(hr^{-1})	(hr^{-1})
Test (A)				
mean	1.2246	0.2142	0.04143	0.0526
CV(%)	81	46	18	17
N	23	30	29	30
Ref. (B)				
mean	0.9706	0.2254	0.04447	0.0543
CV(%)	55	54	19	19
N	21	30	28	30
%diff.	26.2	-5.0	-6.8	-3.1
HALF	(hr)	(hr)	(hr)	(hr)
Test (A)				
mean	1.169	3.761	17.266	13.535
CV(%)	103	33	19	17
N	23	30	29	30
Ref. (B)				
mean	1.059	3.644	16.116	13.253
CV(%)	83	33	18	21
N	21	30	28	30
% diff.	10.4	3.2	7.1	2.1

Balanced study, arithmetic means = least-squares means (LSM)
% diff. = (A - B) *100/B, where A and B are the means
ratio = exp(estimate), where estimate is from the ANOVA
LSM are reported for AUCINF since data sets were incomplete
N = 29

Table 5A - Test/Ref. Ratios for Selegiline and Desmethylselegiline

Subject	Seleg.			DES		
	AUC0-t	AUCINF	CMAX	AUC0-t	AUCINF	CMAX
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

Table 5B - Test/Ref. Ratios for Amphetamine and Methamphetamine

Subject	Amphet.			Metham.		
	AUC0-t	AUCINF	CMAX	AUC0-t	AUCINF	CMAX
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

Table 5C - Summary of T/R Ratios

Analyte	Parameter	N	< 75%	75-125%	> 125%
SEL	AUC0-t	30	7	6	17
	AUCINF	18	4	4	10
	CMAX	30	8	6	16
DES	AUC0-t	30	1	22	7
	AUCINF	30	0	23	7
	CMAX	30	1	21	8
A	AUC0-t	29	2	20	7
	AUCINF	28	3	21	4
	CMAX	29	4	22	3
MA	AUC0-t	30	4	19	7
	AUCINF	30	3	19	8
	CMAX	30	3	19	8

Table 6 - During Study Validation (Fasting)

	Selegiline	DES	A	MA
Standard Curves (N)				
r				
range				
CV(%)				
% nominal				
Low QC				
Conc.				
N				
CV(%)				
% nominal				
Middle QC				
Conc.				
N				
CV(%)				
% nominal				
High QC				
Conc.				
N				
CV(%)				
% nominal				

Table 7 - Prestudy Validation

Parameter	Selegiline	DES	A	MA
LOQ				
Standard Curve Range				
r (N = 3)				
Standards:				
Inter-run				
CV(%)				
% nominal				
QC samples:				
Inter-run				
CV(%)				
% nominal				
Intra-run				
CV(%)				
% nominal				
Recovery (%)				
QC Conc.				
CV(%)				
N				
Stability:				
Frozen[1]				
Low Mean Ratio				
CV(%)				
% nominal				
High Mean Ratio				
CV(%)				
% nominal				
Frozen[4]				
Low Mean Ratio				
CV(%)				
% nominal				
High Mean Ratio				
CV(%)				
% nominal				
Freeze-Thaw[5]				
Low Mean Ratio				
CV(%), N				
High Mean Ratio				
CV(%), N				
Autosampler[6]				
deviation				
N				

Table 7 - Prestudy Validation (continued)

Table 8 - 90% CI's (Fasting Study, Log-transformed Data)

Parameter	Condition 1	Condition 2	Condition 3
AUC0-t			
DES	104.8-114.4	104.8-114.4	104.7-114.7
A	95.7-110.8	95.7-110.8	94.9-110.8
MA	97.1-112.4	97.1-112.4	-
AUCINF			
DES	105.2-114.8	105.2-114.8	105.1-115.0
A	96.8-112.2	96.8-112.3	96.0-111.4
MA	97.2-111.9	97.2-111.9	-
CMAX			
DES	102.0-118.0	102.0-118.0	102.0-118.6
A	93.2-104.8	93.2-104.8	92.8-105.2
MA	97.1-111.8	97.1-111.8	-

Condition 1 Results reported by sponsor
Condition 2 Results obtained by reviewer (sponsor's diskette)
Condition 3 Exclude S16 (DES) and S6 and S27 (A)

Table 9A - Mean Reported Plasma Concentrations of Selegiline (pg/mL, Fed Study)

Time (hr)	Trt A mean[1]	(test fast) CV(%)	Trt B mean[2]	(test fed) CV(%)	Trt C mean[3]	ref. fed) CV(%)	% diff B v. C	% diff B v. A
0	0	-	0	-	0	-	-	-
0.17	46.1[4]	354	96.8	279	27.8[1]	158	248	110
0.33	394.7	146	810.1	192	560.8[2]	131	45	105
0.5	851.5	154	1078[1]	184	944.8[2]	131	14	27
0.67	962.2	118	1043	142	976.7	126	6.8	8.4
0.83	900.8[5]	122	1004[1]	127	1034.5	104	-3	11
1	723.4[5]	103	1227[4]	151	1242.8	125	-1	70
1.17	418.9	115	916.1	147	1127.3	143	-19	119
1.33	314.1	121	921.4	140	938.7[2]	119	-0	193
1.5	320.7[4]	115	921.1[1]	126	1032[2]	110	-11	187
1.75	206.8	134	734.9	111	840.4[2]	95	-13	255
2	151.7	126	696.9[1]	113	731.7[2]	84	-5	359
2.5	104.9[4]	151	381.5[1]	139	299.3[2]	92	27	264
3	60.4[5]	164	341.3	138	214.8[2]	81	59	465
4	41.0[4]	192	155.9[4]	173	110[2]	111	42	280
5	21.2[4]	278	106.3[1]	184	68.5[4]	173	55	401
6	11.5	289	63.6[1]	226	35.2[1]	204	81	453
8	9.1	273	34.3[1]	278	30.3[1]	254	13	277
12	4.9	400	19.2[2]	311	0.00[1]	-	-	-
16	7.5	400	12.6[1]	289	0.00[2]	-	-	-

[1] N = 16 [2] N = 17 [3] N = 18 [4] N = 15 [5] N = 14

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 9B - Mean Reported Plasma Concentrations of Desmethylselegiline (pg/mL, Fed Study)

Time (hr)	Trt A mean[1]	(test fast) CV(%)	Trt B mean[2]	(test fed) CV(%)	Trt C mean[3]	(ref. fed) CV(%)	% diff Bv.C	% diff Bv.A
0	0	-	0	-	0	-	-	-
0.17	117.9	188	152.6	248	67.1	287	127	29
0.33	3124.8	98	2098	160	2993.6	132	-30	-33
0.5	8070.1	67	4386	116	5642.2	90	-22	-46
0.67	9999	44	5932.2	87	7097.3	71	-16	-41
0.83	11375	54	6605.6	72	7709.2	60	-14	-42
1	11052	40	7861	60	8670.2	46	-9	-29
1.17	10207	38	7821.6	58	8461	43	-8	-23
1.33	9015.9	44	8119	53	8154.9	38	-0	-10
1.5	8450.1	51	8468.9	48	9220.9	63	-8	0.2
1.75	7430.1	44	8180	42	8442.6	48	-3	10
2	6701.1	42	7855.1	38	8433.1	38	-7	17
2.5	4970.7	46	6982.9	37	7824.7	37	-11	40
3	4100.8	46	6223.8	42	6297.3	37	-1	52
4	2466	48	4309.1	42	4377	42	-2	75
5	1627.3	46	2809.8	48	3071.4	60	-9	73
6	1223.6	52	1988.3	56	2020.8	58	-2	62
8	776.2	60	1237.9	70	1461.3	101	-15	59
12	327	92	575.2	80	534	54	7.7	76
16	197.4	121	336.6	104	266.2	85	26	71

[1] N = 16 [2] N = 17 [3] N = 18

Trt. A: N = 15 (0.67, 16 hr)
Trt. B: N = 16 (0.17, 0.5, 1 hr)
Trt. C: N = 17 (0.17, 0.33, 2.5, 5 hr); N = 16 (2 hr)

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 9C - Mean Reported Plasma Concentrations of Amphetamine (ng/mL, Fed Study)

Time (hr)	Trt A mean[1]	CV (%)	Trt B mean[2]	CV (%)	Trt C mean[3]	CV (%)	% diff Bv.C	% diff Bv.A
0	0.00	-	0.00	-	0.00	-	-	-
0.5	0.503	74	0.442	180	0.413	128	7.02	-12
1	1.76	28	1.244	74	1.589	69	-22	-29
2	2.835	24	2.363	36	2.945	33	-20	-17
3	2.83	22	3.056	29	3.268	26	-6.5	7.99
4	3.001	22	3.246	26	3.526	33	-7.9	8.16
6	3.425	19	3.306	26	3.715	26	-11	-3.5
8	3.346	17	3.486	25	3.483	24	0.09	4.18
12	2.984	20	3.101	21	3.214	32	-3.5	3.92
16	2.589	21	2.516	25	2.636	26	-4.6	-2.8
24	1.896	30	1.767	19	1.862	28	-5.1	-6.8
36	1.389	38	1.189	25	1.31	42	-9.2	-14
48	0.65	54	0.653	35	0.735	67	-11	0.46
72	0.198	98	0.163	89	0.163	159	0	-18

[1] N = 15 [2] N = 16 [3] N = 18

Trt. A: N = 14 (0.5, 1, 4, 6, 12, 48, 72 hr)
Trt. B: N = 15 (0.5, 16, 36, 72 hr); N = 14 (1 hr)
Trt. C: N = 16 (0.5, 1 hr); N = 17 (2, 72 hr)

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 9D - Mean Reported Plasma Concentrations of Methamphetamine (ng/mL, Fed Study)

Time (hr)	Trt A mean[1]	CV (%)	Trt B mean[2]	CV (%)	Trt C mean[3]	CV (%)	% diff Bv.C	% diff Bv.A
0	0.00	-	0.00	-	0.00	-	-	-
0.5	2.292	82	2.234	173	2.298	108	-2.8	-2.5
1	8.348	30	5.49	72	7.18	58	-24	-34
2	11.04	22	9.879	38	11.52	32	-14	-11
3	10.75	21	11.41	21	11.94	17	-4.4	6.14
4	10.7	17	11.63	16	12.06	19	-3.6	8.69
6	10.83	15	11.63	15	11.85	17	-1.9	7.39
8	10.47	11	10.81	15	10.19	14	6.08	3.25
12	8.567	14	8.864	17	8.5	20	4.28	3.47
16	7.11	22	6.984	28	6.541	19	6.77	-1.8
24	4.525	23	4.36	25	4.22	27	3.32	-3.6
36	3.089	32	2.667	39	2.575	39	3.57	-14
48	1.323	46	1.272	38	1.197	50	6.27	-3.9
72	0.357	108	0.264	127	0.191	171	38.2	-26

[1] N = 15 [2] N = 16 [3] N = 18

Trt. A: N = 15 (0.5, 1, 4, 12, 48, 72 hr)
Trt. B: N = 16 (0.5, 1, 16, 36, 72 hr); N = 14 (1 hr)
Trt. C: N = 16 (0.5, 1 hr); N = 17 (2, 3, , 48, 72 hr)

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 10 - Mean[1] Reported Pharmacokinetic Parameters for Selegiline, DES, A, and MA (Fed Study)

	Selegiline	Desmethyl-selegiline	Amphetamine	Meth-amphetamine
AUC0-t	(pg*hr/mL)	(pg*hr/mL)	ng*hr/mL)	ng*hr/mL)
TFast (A)				
mean	1112.1	31940.3	102.32	278
CV(%)	129	44	28	20
N	16	16	15	16
TFed (B)				
mean	2687.8	38514.9	99.08	272.1
CV(%)	149	45	17	20
N	17	17	16	17
Rfed (C)				
mean	2302.9	41140.5	103.44	261.4
CV(%)	86	33	26	20
N	18	18	18	18
% Diff.[2]				
B v. C	17	-6.4	-4.2	4.1
B v. A	232	20.6	-3.2	-2.1
AUCINF	(pg*hr/mL)	(pg*hr/mL)	(ng*hr/mL)	(ng*hr/mL)
TFast (A)				
mean	1368.2	33428.2	114.26	299
CV(%)	119	46	25	18
N	11	16	15	16
TFed (B)				
mean	3544.1	40811.6	109.68	290
CV(%)	138	47	18	19
N	12	17	16	17
Rfed (C)				
mean	2574	42767.1	125.04	285.8
CV(%)	83	33	41	23
N	15	18	18	18
% Diff.				
B v. C	38	-4.6	-12.2	1.5
B v. A	159	22	-4.0	-3.0
CMAX	(pg/mL)	(pg/mL)	(ng/mL)	ng/mL)
TFast (A)				
mean	1220.7	13724.7	3.6463	12.1655
CV(%)	105	38	17	17
N	16	16	15	16
Tfed (B)				
mean	1854	10753.2	3.7524	12.9717
CV(%)	108	38	22	14
N	17	17	16	17
Rfed (C)				
mean	1920.2	12332	3.9371	13.3331
CV(%)	96	42	26	20
N	18	18	18	18
% Diff.				
B v. C	-3.4	-12.8	-4.7	-2.7
B v. A	52	-21.6	2.9	8.6

TMAX	(hr)	(hr)	(hr)	(hr)
TFast (A)				
mean	0.698	0.876	6.467	4.125
CV(%)	48	38	41	54
N	16	16	15	16
Tfed (B)				
mean	1.382	1.746	7.313	4.412
CV(%)	83	62	44	38
N	17	17	16	17
Rfed				
mean	0.935	1.259	6.167	4
CV(%)	49	45	56	41
N	18	18	18	18
% Diff.				
B v. C	48	39	18.6	10.3
B v. A	98	99	13.1	7.0

KEL	(hr^{-1})	(hr^{-1})	(hr^{-1})	(hr^{-1})
TFast (A)				
mean	1.2281	0.2793	.04288	.05179
CV(%)	46	35	24	27
N	11	16	15	16
TFed (B)				
mean	0.9118	0.2482	.04284	.05206
CV(%)	66	39	22	21
N	12	17	16	17
Rfed (C)				
mean	0.9922	0.2536	.04212	.05292
CV(%)	43	27	31	21
N	15	18	18	18
% Diff.				
B v. C	-8.1	-2.1	1.7	-1.6
B v. A	-25.7	-11.1	-0.1	0.52

HALF	(hr)	(hr)	(hr)	(hr)
TFAst (A)				
mean	0.753	2.788	17.044	14.243
CV(%)	68	35	24	26
N	11	16	15	16
TFed (B)				
mean	1.373	3.186	17.01	13.845
CV(%)	105	35	24	20
N	12	17	16	17
Rfed (C)				
mean	0.838	2.922	18.765	13.721
CV(%)	46	26	47	23
N	15	18	18	18
% Diff.				
B v. C	64	9.0	-9.4	0.9
B v. A	82	14.2	-0.2	-2.8

[1] arithmetic means
[2] % diff. = (T - R) *100/R, where T and R are the means

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 11 - Reported Least Squares Means (LSM) and Ratios[1] for Selegiline, DES, A, and MA (Fed Study)

Analyte	Selegiline	DES	A	MA
AUC0-t	pg*hr/mL	pg*hr/mL	ng*hr/mL	ng*hr/mL
LSM				
Trt. A	1632.92	34781	102.54	267.2
Trt. B	2503.46	41224	102.54	273.4
Trt. C	2449.63	38991	101.57	262.2
Ratio	0.741	1.038	1.029	1.049
AUCINF	pg*hr/mL			
LSM				
Trt. A	1218.39	36392	115.88	289.1
Trt. B	3132.96	43551	112.58	289.3
Trt. C	2688.78	40670	120.4	286.2
Ratio	0.768	1.045	0.96	1.017
CMAX	pg/mL			
LSM				
Trt. A	1183.51	13592	3.7082	11.9188
Trt. B	1744.93	11429	3.8829	13.4898
Trt. C	2151.94	11907	3.8485	13.0586
Ratio	0.771	0.989	1.026	1.053

[1] ratios are expressed as the antilog of the geometric means

Trt. A = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fasted
Trt. B = selegiline HCl 10 mg (2 X 5 mg tablet), Lederle, fed
Trt. C = Eldepryl® 10 mg (2 X 5 mg tablet), Somerset, fed

Table 12 - Ratios[1] (Test, fed/Ref., fed) of Geometric Means

Analyte	N	Condition	logAUC0-t	logAUCINF	logCMAX
DES	19	1	1.038	1.045	0.989
	19	2	1.038	1.045	0.989
	13	3	1.020	1.026	1.033
	13	4	1.020	1.026	1.033[2]
	13	6	-	1.046	-
A	19	1	1.029	0.960	1.026
	19	2	1.029	0.960	1.026
	13	3	1.080	0.974	1.059
	13	4	1.080	0.974	1.059
	13	5	1.028	0.924	0.994
	13	6	-	1.021	-
	12	7	1.027	0.948	1.026
MA	19	1	1.049	1.017	1.053
	19	2	1.050	1.017	1.053
	13	3	1.060	1.010	1.021
	13	4	1.060	1.010	1.021
	13	5	1.043	1.003	0.956
	12	7	1.008	0.988	0.981

Condition 1 Reported values using sponsor's model (SUBJ, PER, TRT, RESIDA, RESIDB)
2 Reviewer's results using diskette data and sponsor's model
3 Data from 13 subjects completing 3 phases using sponsor's model
4 Reviewers's results using Condition 3 data and model SEQ, SUBJ(SEQ), PER, TRT, RES1
5 Exclusion of Trt. A and standard model
6 Exclusion of inestimable λ_z values
7 Exclusion of S5 from A and MA data

[1] Antilog(estimate) using log-transformed data
[2] Statistically significant first-order residual effect ($p < 0.1$)